



Canadian Patent

Brevet canadien

1317881

To all to whom these presents shall come:

Whereas a petition has been presented to the Commissioner of Patents praying for the grant of a patent for a new and useful invention, the title and description of which are contained in the specification of which a copy is hereunto attached and made an essential part hereof, and the requirements of the Patent Act having been complied with.

Now therefore the present patent grants to the applicant whose title thereto appears from the records of the Patent Office and as indicated in the said copy of the specification attached hereto, and to the legal representatives of said applicant for a period of seventeen years from the date of these presents the exclusive right, privilege and liberty of making, constructing, using and vending to the others in Canada the invention, subject to adjudication in respect thereof before any court of competent jurisdiction.

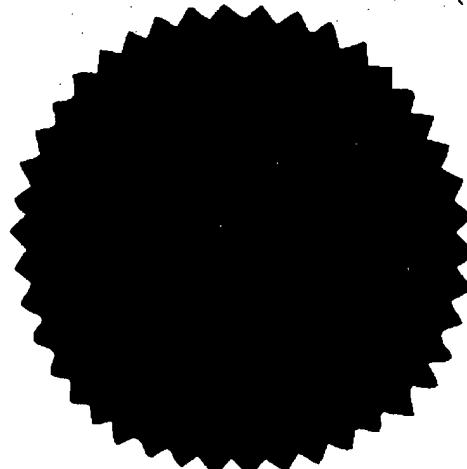
Provided that the grant hereby made is subject to the conditions contained in the Act aforesaid.

All patents are subject to annual maintenance fees subsequent to the modified Patent Act.

In testimony whereof, these letters patent bear the signature of the Commissioner and the seal of the Patent Office hereunto affixed at Hull, Canada.

This Patent was issued on:

MAY
MAI 18 1993
Date _____



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A tous ceux qui les présentes verront:

Considérant qu'une requête a été présentée au Commissaire des brevets, demandant la délivrance d'un brevet pour une invention nouvelle et utile, dont le titre et la description apparaissent dans le mémoire descriptif et dont copie est annexée aux présentes et en fait partie essentielle, et que ladite requête satisfait aux exigences de la Loi sur les brevets.

A ces causes, le présent brevet confère au demandeur dont le titre de propriété dudit brevet est établi d'après les dossiers du Bureau des brevets et est indiqué dans ladite copie du mémoire descriptif ci-annexée, et aux représentants légaux dudit demandeur, pour une période de dix-sept ans, à compter de la date des présentes, le droit, la faculté et le privilège exclusifs de fabriquer, construire, exploiter et vendre à d'autres, au Canada l'invention, sauf jugement en l'espèce par un tribunal de juridiction compétente.

La concession faite par les présentes étant soumise aux conditions contenues dans la loi précitée.

Des frais annuels de maintien seront applicables pour tout brevet octroyé subséquemment à la Loi modifiant la Loi sur les brevets.

En foi de quoi, ces lettres patentes portent la signature du Commissaire ainsi que le sceau du Bureau des brevets apposé à Hull, Canada.

Ce Brevet a été délivré le:

Commissioner of Patents - Commissaire des brevets





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(19) (CA) CANADIAN PATENT (12)

(54) Aerosol Compositions for Nasal Delivery of Vitamin B₁₂

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This invention is concerned with aerosol compositions for nasal administration of a vitamin B₁₂ to a human suffering a vitamin B₁₂ deficiency. It is concerned also with methods of administering such compositions.

Cyanocobalamin is a vitamin B₁₂, and is one of the B₁₂ class of vitamins which includes vitamin B_{12a} (hydroxocobalamin), vitamin B_{12b} (aquacobalamin), vitamin B_{12c} (nitrilocabalamin), coenzyme B₁₂ (5'-deoxyadenosine cobalamin) and methyl B₁₂ (methyl cobalamin). Cyanocobalamin is the principal member of the class, and the most widely employed in medicine. This invention will be described as it relates to cyanocobalamin, but those skilled in the art will recognize that the invention is applicable to the class.

Vitamin B₁₂ is an essential compound for normal growth, hematopoiesis, production of all epithelial cells and maintenance of myelin throughout the nervous system. It was first isolated from liver concentrate by Rickes and his coworkers in 1948 and structurally elucidated by Hodgkin and her coworkers in the late 1950's. It is currently commercially available as a tablet and as an injectable.

Therapeutically, vitamin B₁₂ is employed in the treatment of a variety of B₁₂ deficiency afflictions, principally anemias such as pernicious and *Diphyllobothrium latum*. Although the minimum daily requirement of vitamin B₁₂ is approximately 0.1ug, the generally prescribed initial therapeutic dose is 100 to 1000ug given intramuscularly. Maintenance therapy with vitamin B₁₂ is usually 100ug intramuscularly, monthly and must be continued for life.



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Since pernicious anemia is often a disease of later years when many sufferers have reduced muscle mass or are atrophic, repeated intramuscular injections of vitamin B₁₂ can be inconvenient, painful and often require doctor's visits. In some cases at least in the early stages, hospitalization is required. As a result, there is a need for a more convenient, less painful and less expensive method of administering vitamin B₁₂, particularly one that would not require hospitalization or repeated physician contacts.

Unfortunately, up to the present time no efficient method of administering B₁₂ which will achieve therapeutically useful blood levels of the vitamin except parenteral administration has been devised.

In 1953 and 1954 Monto et al in Am. J. Med. Sci., 223, 113 (1953) and Arch. of Int. Med. 93, 219 (1954) described administration of B₁₂ by nasal inhalation and instillation. The vehicles for administration were aqueous isotonic sodium chloride solution and lactose powder. Although the results were reported as effective, safe and economical, the fact is that parenteral administration remains the only method regarded by the medical community as a safe, reliable and effective method for treating vitamin B₁₂ deficiencies in humans. No composition for nasal inhalation or instillation has become commercially available for nasal administration to mammals. There have been no published descriptions of compositions for nasal administration of a vitamin B₁₂ by aerosol techniques of which applicant is aware.

The difficulty with nasal instillation by nasal dosage as the procedure is described in the cited articles is that most of the B₁₂ passes immediately into the throat. It is

not in contact with the nasal mucosa for a sufficient period of time to permit useful and uniform absorption. Most of the B₁₂ so administered is, in fact wasted.

Aerosol compositions have now been discovered for the nasal administration of B₁₂ which provide a medication to keep the B₁₂ in contact with the nasal mucosa for an extended period of time. During the time the compositions are in such contact, the B₁₂ is uniformly absorbed from the compositions through the nasal mucosa and is then uniformly distributed systemically. The use of the compositions, because of the efficiency with which the B₁₂ is absorbed allows the use much lesser amounts of B₁₂ than is normally present in parenteral B₁₂ compositions. Moreover, since the patient can self administer the B₁₂, the need for hospitalization or physician contacts is minimized and may even be eliminated.

This invention provides vitamin B₁₂ containing aerosol compositions specifically formulated for nasal administration which will retain the B₁₂ in contact with the nasal mucosa for a sufficiently long period of time to permit consistent, continuous and uniform absorption of therapeutically effective amounts of a vitamin B₁₂ through the nasal mucous membrane.

The invention, therefore comprises aerosol compositions containing a therapeutically effective amount of a vitamin B₁₂. More specifically it comprises therapeutic compositions in aerosol form for nasal administration. The B₁₂ is in an isotonic aqueous buffer and is sealed in a container equipped with a metering valve which when actuated will provide a spray of particles in which the particle size of the droplets of the spray is from 5 to 50 microns. The invention also comprises the method of using the compositions to treat humans afflicted with a vitamin B₁₂ deficiency.

The pH of the compositions of the invention is from about 4 to 6. At this pH, B₁₂ is stable so that the compositions have a shelf life which may be a year or more. Additionally, at this pH, irritation of the nasal mucosa is minimal. The pH is maintained with a physiologically acceptable buffer composition suitably an acetate, phosphate, phthalate, borate, or other buffer.

An acetate buffer is preferred for convenience and economy.

The isotonicity of the composition is accomplished using sodium chloride, or other pharmaceutically acceptable agent such as dextrose, boric acid, sodium tartrate or other inorganic or organic solute. Sodium chloride is preferred particularly for buffers containing sodium ions.

The compositions of this invention may contain a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of humectants can be employed including, for example sorbitol, propylene glycol or glycerol. The concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

An enhanced absorption of B₁₂ across the mucous membrane may be accomplished employing a surfactant. Typically useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80*, Polyoxy 40 Stearate*, Polyoxyethylene 50 Stearate* and Octoxynol*. The usual concentration is from 1% to 10% based on the total weight.

* trade-mark

A preservative may be employed to increase the shelf life of the compositions. Benzyl alcohol is suitable, although a variety of preservatives including, for example, Parabens, thimerosal, chlorobutanol, or benzalkonium chloride may also be employed. A suitable concentration of the preservative will be from 0.02% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

The compositions of the invention are dispensed from a sealed container equipped with a metering valve which when actuated releases a spray in which the particle size of the spray droplets is from about 5 to 50 microns, preferably 10 to 20 microns. It has been found that if the spray droplets are below this range, they go directly through the nasal passages into the lungs. If they are larger, they coalesce into large drops which either run out of the nose or down into the throat.

Suitable containers and metering valves are available commercially and need not be described here. They are available for use in packaging systems which deliver the aerosol compositions by all of the conventional aerosol techniques. These include mechanical pumps in which delivery is made by movement of a piston; compressed air mechanisms in which delivery is made by hand pumping air into the container; compressed gas techniques in which delivery is made by the controlled release of a compressed gas in the sealed composition; and liquid propellant techniques in which a low boiling liquid hydrocarbon or halohydrocarbon is vaporized to exert a pressure and force the aerosol composition through the metered valve. All of these systems are useful in the practice of this invention.

The most widely employed compressed gas for delivering aerosol compositions is nitrogen. The principal hydrocarbon is butane, although other low boiling hydrocarbons can be used in pure or mixed form. Fluorocarbons of the Freon series are useful in the invention. These include, for example, Freon 11, 12 and 14 and Fluorocarbon-FC152A.

All of the foregoing systems and propellants are useful for the nasal administration of the aerosol compositions of this invention.

Due to the efficiency with which B₁₂ is absorbed from the compositions of this invention, a therapeutically effective amount of B₁₂ for nasal administration will normally be appreciably less than for conventional methods of administration. Typically the concentrations of B₁₂ in the compositions of this invention will be from about 0.05% to 1% by weight based on the total weight. The concentration may vary considerably however with the selected method of delivery. If the composition is a simple aqueous solution of B₁₂, possibly including excipients in solution or suspension under a compressed gas, the preferred concentration will be within the above range. But if the composition also contains propellants, the concentration of B₁₂ might vary. The important point is that the concentration be selected so that, acting together with the selected metering valve, each spray will deliver a dosage unit of from about 50 to 1000 micrograms. It is of course possible to design an equivalent combination of concentration and metering valves so that a dosage unit containing 50 to 1000 micrograms of B₁₂ is delivered by two, three or even more valve actuations and resulting sprays.

The following aerosol compositions of this invention are useful for delivery by compressed gas systems or by mechanical pumps.

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Benzalkonium Chloride NF	0.020 g
Thimerosal USP	0.002 g
Acetic Acid NF	0.100 g
Sodium Acetate (Anhydrous) USP	0.270 g
Sodium Chloride USP	0.820 g
Cyanocobalamin USP	0.200 g
Water, Purified USP	q.s. 100.000 ml

Phenylmercuric Acetate NF	0.002 g
Acetic Acid NF	0.100 g
Sodium Acetate (Anhydrous) USP	0.270 g
Boric Acid NF	1.740 g
Cyanocobalamin USP	0.500 g
Water, Purified USP	q.s. 100.000 ml

Benzalkonium Chloride NF	0.020 g
Phenylmercuric Acetate NF	0.002 g
Acetic Acid NF	0.100 g
Sodium Acetate (Anhydrous) USP	0.270 g
Boric Acid NF	1.740 g
Cyanocobalamin USP	1.000 g
Water, Purified USP	q.s. 100.000 ml

Other compositions of this invention are produced by dissolving the B₁₂ in a solvent which is miscible with the selected propellant and taking the solution up in the propellant. The resulting solution is sealed in an appropriate container having a metered valve. Suitable solvents include, for example, ethylene glycol and polyethylene glycol. When the valve is actuated the B₁₂ is expelled in the solution and deposits on the nasal mucosa.

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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A therapeutic composition in aerosol form for nasal administration and absorption essentially through the nasal mucous membrane comprising a therapeutically effective amount of a vitamin B₁₂ in an isotonic aqueous buffer at a pH of from about 4 to 6 in an aerosol formulation in a sealed container equipped with a metering valve which when actuated provides a spray of particles in which the particle size is from about 10 to 50 microns.
2. A therapeutic composition of claim 1 wherein the vitamin B₁₂ is cyanocobalamin.
3. A composition as in claim 1 or 2 wherein the spray particle size is 10 to 20 microns.
4. A therapeutic composition in aerosol form for nasal administration and absorption essentially through the nasal mucous membrane containing a vitamin B₁₂ in an isotonic aqueous buffer at a pH of from about 4 to 6 in an aerosol formulation in a sealed container equipped with a metering valve which when actuated provides a spray of particles in which the particle size is from about 10 to 50 microns each separate spray containing from 50 to 1000 micrograms of vitamin B₁₂.
5. A therapeutic composition as in claim 4 wherein the vitamin B₁₂ is cyanocobalamin.
6. A therapeutic composition as in claim 4 or 5 wherein the spray particle size is 10 to 20 microns.
7. A therapeutic composition in aerosol form comprising a therapeutically effective amount of a vitamin B₁₂ in an isotonic aqueous buffer at a pH of from 4 to 6 in a sealed container capable of delivering a spray of particles in which the particle size is from about 10 to 50 microns

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for the use of nasal administration to a human afflicted
with vitamin B₁₂ deficiency.

8. A therapeutic composition as in claim 7 wherein
the vitamin B₁₂ is cyanocobalamin.

9. A therapeutic composition as in claim 7 or 8
wherein the particle size is from 10 to 20 microns.



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